

Vitamin D as an Immunological Factor in Combating COVID-19

Eliana dos Santos Farias¹, Dayana Ferraz da Silva², Valdir Silva da Conceição³, Angela Machado Rocha⁴

^{1,2}Bachelor of Biotechnology from the Federal University of Bahia, Salvador, Bahia, Brazil

³Master's student of the Graduate Program in Intellectual Property and Technology Transfer for Innovation at the Federal University of Bahia, Institute of Chemistry, Salvador, Bahia, Brazil

⁴PhD in Energy and Environment from the Federal University of Bahia, Professor at the Institute of Health Sciences at the Federal University of Bahia (ICS-UFBA), from the Graduate Program in Intellectual Property and Technology Transfer for Innovation (ProfNIT) Focal Point from the Federal University of Bahia, Salvador, Bahia, Brazil

Abstract— The world is facing the worst pandemic caused by the new coronavirus (COVID-19) since the end of 2019, which started in China and continued to spread over the world. Several studies confirmed that when the immune system is strengthened, it is able to modulate the immune response at the time of infection, reducing the amount of proinflammatory cytokines. Vitamin D participates in the absorption of calcium by the body, which contributes to bone health and also facilitates the absorption of other vitamins. This article highlights about the role of vitamin D to the immune response. The methodology used was the qualitative and descriptive approach. It is concluded by the studies carried out that vitamin D reduces the chance of respiratory infections and can be another element to be used to combat contamination by COVID-19.

Keywords— Coronavirus, Pandemic, Immune System, Health, Vitamin Absorption.

I. INTRODUCTION

The main function of vitamin D is the regulation of calcium homeostasis, contributing to bone formation and resorption, through its interaction with the parathyroid, kidney and intestines. These are all involved in the immune system, regulating the differentiation of lymphocyte cells and interfering with the production of cytokines, which are the proteins that cells release. They also increase body temperature in response to infection or inflammation, producing fever as a defense mechanism to stop the virus reproducing [1, 2, 3, 4]. According to the level of vitamin D found in the body, there is a classification made by the scientific community which are as follows: vitamin D deficiency, insufficiency and sufficiency [5].

Some studies show that patients with autoimmune diseases have low concentrations of calcitriol and when they are supplemented with vitamin D, there is a clinical improvement [6]. The relationship between the serum vitamin D level and the severity of COVID-19 (Corona Virus and Disease 19) has been discussed worldwide, due to a pandemic alerted by the World Health Organization - WHO, in March 2020. Research into alternatives to treat

people contaminated with COVID-19 indicate that vitamin D can this is because in addition to its homeostasis function, it participates in the regulation of the immune system and manages to destroy viruses in the body through cathelicidin [7, 8, 9, 10, 11].

The influenza virus affects the respiratory tract by direct viral infection or damage to the immune system's response. This can cause death due to the resulting pneumonia and there is a higher probability of this occurring in patients under the age of five and over 65 years of age, residents in nursing home, those admitted to hospitals with chronic lung or heart disease, those with a history of smoking and immune-compromised individuals [9, 10, 11].

Seasonal influenza infections typically peak in winter, as this is the period when doses of sun and concentrations of 25-hydroxyvitamin D {25 (OH) D} or calcitriol are at their lowest, especially among people residing in countries at medium and high altitudes. Also during this period, there are low temperatures and low relative humidity, both of which contribute to the survival of the influenza virus for longer outside the human body, compared warmer periods. One of the ways to reduce the risk of developing influenza

in winter is to increase concentrations of 25 (OH) D, using vitamin D supplementation. Some studies show a 27% reduction in influenza-like diseases [9, 11, 12] with this.

In winter, the low levels of vitamin D enable viral epidemics among people not taking Vitamin D supplements. These tend to reduce serum concentrations of 25 (OH) D i.e. Vitamin D which has the ability to reduce the risk of viral diseases. High concentrations of 25 (OH) D have the power to reduce the risk of several chronic diseases such as cancer, cardiovascular diseases, diabetes, chronic respiratory tract infections, among others [9, 11, 13]. It also reduces the risk of urinary tract infections through the following mechanisms: "maintaining tight junctions, killing viruses involved in the induction of cathelicidin and defensins and reducing the production of pro-inflammatory cytokines by the innate immune system, thereby decreasing the risk of a storm cytokines lead to pneumonia" [9, 11].

Elderly people belong to one of the groups at risk, especially those who live in nursing homes and who are deprived of exposure to sunlight. They often also have inadequate nutrition and interactions with medications, and for these reasons tend to have vitamin D deficiency [9, 11, 13, 14].

Coronavirus is a pathogen known since the 1960s and has the power to infect humans and other vertebrate animals. In humans, they attack the respiratory and / or gastrointestinal systems, ranging from a simple flu to a more serious infection such as pneumonia. There is an increase in the inflammatory response that resembles several autoimmune diseases and in patients trigger an imbalance in the production of pro-inflammatory cytokines, causing the disease to worsen [15, 16, 17, 18, 20].

Among the possible hosts of COVID-19 is the bat, the same animal responsible for the appearance of the Severe Acute Respiratory Syndrome (SARS) that occurred in 2002 [8, 15, 19].

II. METHODOLOGY

The present study was carried out from a literature review, addressing topics related to COVID-19, vitamin D and the association between these two items.

The research was exploratory in character, to gain a certain familiarity with the studied themes, collaborating for the improvement of ideas, in order to obtain a greater understanding of the various aspects related to the studied theme [20].

In order to collect data, literature research was carried out using scientific articles, theses, dissertations, essays and

specialized sites on the subject and with the help of material already published at scientific events, in magazines, newspapers, books, among others [20].

III. THEORETICAL FOUNDATION

3.1 VITAMIN D METABOLISM

Vitamin D is a steroid hormone that is present in living beings. It can be obtained in two ways: endogenous production which is due to sun exposure and exogenous so obtained through diet and fortified foods. It is understood as a fat-soluble compound, which can be obtained by skin synthesis in the presence of ultraviolet light, when the 7-dehydrocholesterol compound changes to cholecalciferol (D3). In plants, this process also occurs by transforming ergosterol into ergocalciferol (D2) [13, 14, 21]. A reduction in vitamin D in humans can be related to the following factors: age, skin pigmentation, altitude, time of sun exposure and food intake. The need to expose the body to solar radiation was verified at the time of the Industrial Revolution. Workers confined in factories for long hours of labour were not exposed to sufficient sunlight, causing disease, especially rickets [14, 22].

The chemical structure of vitamin D2 differs from that of D3 in that it has an additional double bond and a methyl group incorporated into the long side chain of vitamin D2. Vitamin D derived from the diet is absorbed together with fats in the small intestine. This is aided by bile generated in the liver, while in the endogenous bile, metabolism occurs in the liver. About 80-90% of vitamin D metabolism occurs through endogenous synthesis and only 10-20% occurs through diet. Foods rich in vitamin D include: herring, tuna, mackerel, salmon, sardines, beef liver, chicken and cod, egg yolk, cabbage and mushrooms [1, 3, 4, 14, 23].

Vitamin D undergoes photolysis to become biologically active, and the conversation begins with the endogenous synthesis of vitamin D in the epidermis, after sun exposure, where 7-dehydrocholesterol (7-DHC) is found, which is vitamin D3, a cholesterol precursor. The activation of vitamin D begins with the absorption of the photon of ultraviolet radiation B (UVB) by 7-DHC, promoting the photolytic breakdown, resulting in the formation of pre-vitamin D3. This is then transported in the blood by a glycoprotein, the protein binding vitamin D (DBP), and this coupling to DBP is directed to the liver. However, pre-vitamin D3 undergoes hydroxylation mediated by the microsomal enzyme of the cytochrome P450 superfamily (CYP450), known as CYP2R1 (cytochrome P450 family 2, subfamily R, member 1), forming 25-hydroxyvitamin D or calcidiol [25 (OH) 2D3]. 25-hydroxyvitamin D bound to

DBP, which is carried to the kidney. The enzyme 1- α -hydroxylase (CYP27B1) promotes hydroxylation by forming 1- α , 25-dihydroxyvitamin D [1,25 (OH) 2D or calcitriol], which is the metabolically active molecule. The expression 1- α – hydroxylase is distributed in several cells of the human body and can be hydroxylated in these locations [3, 14, 23, 24, 25, 26, 27].

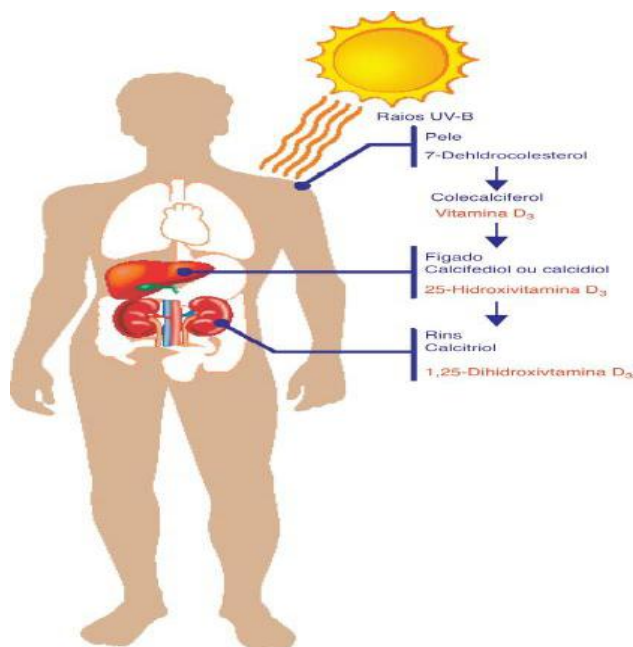


Fig. 1: Vitamin D metabolism and nomenclature

Source: Lichtenstein et al., (2013)

The radiation actions of the type B ultraviolet ray (UVB) of the sun produces vitamin D₃ in the skin, reaching 7-dehydrocholesterol, which subsequently generates a thermal reaction. In the next step, vitamin D₃ or oral vitamin D is converted to 25 (OH) D in the liver and then to the active metabolite of vitamin D, 1,25 (OH) 2D in the kidneys or other organs as needed. The major effect of part of vitamin D arises from calcitriol, which is introduced into the nuclear vitamin D receptor. This is a DNA-binding protein, which interacts directly with regulatory sequences close to the target genes and which invokes the active chromatin complexes, which genetically and epigenetically contribute to transcriptional production [9, 11, 28].

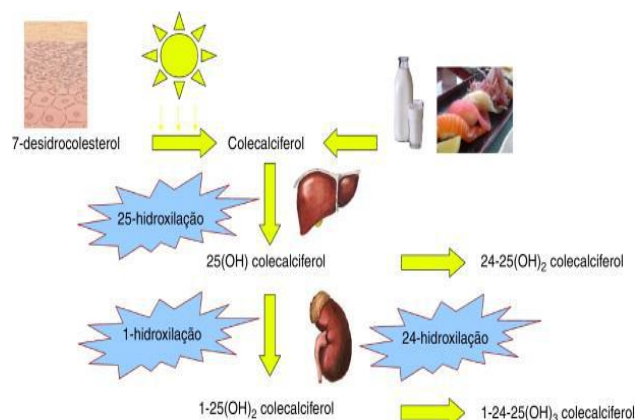


Fig. 2: Vitamin D synthesis and metabolism

Source: Bellan, Pirisi, Sainaghi, (2015)

3.2 VITAMIN D ACTION IN THE IMMUNOLOGICAL SYSTEM

Recent research has found that the vitamin D receptor (VDR) is widely expressed in immune cells present in immature cells, in mature CD8 T lymphocytes, in the thymus, in monocytes, in macrophages, in dendritic cells, in NK cells and in lymphocytes T and B. It is known that VDR modulates the immune response by autocrine and paracrine pathways, culminating in an increase in the innate immune response, associated with a regulation of the acquired response [3, 29].

Vitamin D inhibits the maturation and differentiation of dendritic (DC) cells, inducing a reduction in the expression of molecules of the main class II histocompatibility complex (MHC-II). It also modulates the expression of co-stimulatory molecules CD40, CD80 in monocytes and CD86 and the expression of inflammatory cytokines [IL-1 (interleukin 1), IL-6 (interleukin 6), INF (interferon), IL-8 and IL-12]. Calcitriol also acts in the regulation of B lymphocyte differentiation by raising IL-4 and favoring the change of class to IgE. In addition, 1,25 (OH) 2D directly modulates the proliferation of plasma cells, memory B lymphocytes and induces the apoptosis of immunoglobulin-producing cells. In rheumatic diseases mediated by T lymphocytes, calcitriol has been proven to be an effective alternative in controlling the disease [3, 29, 30, 31].

Evidence shows the possible association of vitamin D with some rheumatic diseases, a classic example being rheumatoid arthritis, whose pathophysiology involves a subpopulation of Th1 cells. Another disease that also has the target pathophysiology of calcitriol immunosuppression is systemic lupus erythematosus (SLE). For patients with SLE who have multiple risk factors for 25 (OH) D deficiency, it has been consistently demonstrated that vitamin D deficiency culminates in decreased immune

tolerance, allowing the development of the autoimmune disease in genetically predisposed individuals [32, 33].

Studies both in vitro and in vivo have demonstrated the immunomodulatory role of calcitriol and how supplementation with vitamin D has improved the clinical status of patients. Epidemiological data demonstrate the correlation between low serum vitamin D levels and the clinical manifestations of autoimmune diseases [33, 34, 35].

Several studies have shown that patients with SLE, RA and MS have low concentrations of calcitriol in the body, and the occurrence of this anomaly triggers the worsening of their clinical condition. When patients were supplemented with vitamin D, they showed clinical improvement over patients who were not. With supplementation, there was an improvement in the levels of inflammatory markers, a preferential growth of naive CD4 + T cells and an increase in Treg and Th2 cells. There was a decrease in effector T cells (Th1 and Th17), memory B cells and anti-DNA antibodies and they had an immunosuppressive action, thus controlling the disease activity [5, 36, 37].

3.3 CORONAVIRUS

COVID-19 is a diverse group of an RNA virus from the Betacoronavirus group, genus coronaviridae, subgenus sarbecovirus and subfamily Orthocoronavirinae. It makes use of a wide variety of vertebrate hosts, which cause the individual to have symptoms ranging from mild to severe intensity, with the potential to cause death. The difference between COVID-19 and other recent viral epidemics is as follows: it is more widespread than Severe Acute Respiratory Syndrome, more infectious than seasonal flu and its mortality is higher than that caused by Ebola. The coronavirus and the flu have some similar characteristics: they are viruses whose peak normally occurs in winter, causing deaths due to the resulting pneumonia. Coronavirus can survive outside the body on surfaces or objects for example. On aluminum and paper, it can survive up to two hours, however, on plastic and stainless steel, it can survive up to 72 hours, according to measures taken at normal room temperature. At a temperature between 30°C and 40°C, there is a drop in survival time, however, at a temperature of 4°C, it can survive up to 28 days [8, 9, 10, 15, 18, 19, 38].

Coronaviruses received this name due to their shape in the form of a crown of protein peaks on their surface. Seven viruses have been identified in the group of coronaviruses that cause human diseases and these are as follows: HCoV-229E; HCoV-OC43; SARS-CoV; HCoV-NL63; HCoV-HKU1; MERS-CoV and SARS-CoV-2 [8, 15, 38, 39].

In the sequencing of the SARS-CoV-2 genome, its similarity to the bat virus was observed of about 96.2%. For this reason it is suspected that the bat is the natural host that originated the virus and that transmission has been caused by it, through unknown intermediate hosts capable of infecting humans [10, 11, 19].

The SARS-CoV-2 epidemic officially began in December 2019 in China, in the city of Wuhan, capital of Hubei province. This is a city larger than London or New York. The name of the “2019 coronavirus disease” was abbreviated to COVID-19, from the English Coronavirus Disease. It is believed that the pandemic started in September 2019, with the maximum peak occurring on February 13, 2020 with 15,141 people infected and with the occurrence of 254 deaths [7, 8, 9, 18, 19].

The spread and death rate in China and South Korea may be associated with low serum concentrations of 25 (OH) D, especially in winter. In China, between July 2013 and February 2014, postmenopausal women showed values of 14 ng / ml, while in South Korea, between October 2011 and May 2014, at mean serum concentrations of 25 (OH) D for elderly people over 60 years of age were ~ 18 ng / ml for men and ~ 15 ng / ml for women [9, 11].

COVID-19 spreads through the respiratory tract through droplets, respiratory secretions and direct contact. The incubation period varies from 2 to 14 days. The most common symptoms reported in confirmed cases are fever, a dry cough and general malaise in most cases, in addition to fatigue, sputum production, dyspnoea, sore throat, headache, earache, chills, muscle pain, loss of smell and taste, shortness of breath and analgesia or arthralgia. The elderly and people with underlying health disorders such as hypertension, diabetes, cardiovascular disease and chronic obstructive pulmonary disease are those more vulnerable to develop acute respiratory distress syndrome, septic shock, metabolic acids and coagulation dysfunction, which can lead to the death of the patient [8, 9, 10, 11, 15, 18, 19, 38].

IV. DISCUSSIONS AND RESULTS

A survey of the most frequent laboratory abnormalities in patients with COVID-19 enable a better understanding of the relationship with the risk factors that lead to the worsening of the disease. In most cases there is an increase in the white blood cell count, neutrophils, lactate dehydrogenase (LDH), alanine aminotransferase (ALT), aspartate aminotransferase (AST), C-reactive protein (PCR), total bilirubin, creatinine, cardiac troponin, increased D-dimer, procalcitonin, longer prothrombin time (PT), a decreased lymphocyte count and albumin [40, 41].

Cathelicidin is regulated by vitamin D or CYP27B1 (family 27 of cytochrome P450, subfamily B, member 1) and is present in neutrophil granules, monocytes, Nk cells. B cells play an important role in the inhibition of viruses and bacteria. Cathelicidin has the ability to break the lipid envelope of the virus and can block viral entry. The CYP27B1 gene is highly expressed in pulmonary epithelial cells in the case of viral respiratory infections at 1.25 (OH) 2D. This increases the level of the TLR CD-14 co-receptor, cathelicidin and the I κ B α induction that acts as an NF- κ B, causing a viral decrease in inflammatory genes to occur [42].

Research carried out in patients with autoimmune diseases measured the increase in the inflammatory response and found that they had low serum vitamin D levels and, from

the moment they were supplemented, improvements in the clinical picture began to appear. The serum concentration of 25 (OH) D above 30 ng / ml is recommended for the population. However, there are several factors that tend to influence concentrations below what is recommended, among which the winter period stands out. Due to lower exposure to the sun, there is a decrease in serum concentration. Right now the vast majority of people are in quarantine and consequently will have a lower vitamin D [9, 10, 11]. Wimalawansa et al. (2020) suggest that people should take an oral daily dose of between 200-300 IU of vitamin D because if the person is infected, they may have fewer complications compared those with a vitamin D deficiency.

Table. 1: Controlled studies of vitamin D-based treatment to prevent respiratory tract infections and influenza.

Item	Researcher				
	Rehman	Avenell <i>et al.</i>	Li-Ng <i>et al.</i>	Urashima <i>et al.</i>	Aloia e Li-Ng
Period	1.5 month	24 months	3 months	4 months	36 months
Type of evaluation	NRCT	RCT	RCT	RCT	RCT
Test group criteria	> 6 respiratory infections in the previous 6 months	Outpatient, age > 70 years	Outpatient, 18-80 years	School children, 6 to 15 years old	African American women in post-menopause
Test population	27 (children, of both sexes, aged between 3 and 12 years)	1740 (70 years old or over, 85% women)	78 (78.2% female, mean age 59.3)	167 (43% female, average age 10.0)	104 (100% female, median age 61.2)
Control population	20 (corresponding children, age and sex)	1704 (age over 70, 85% female)	70 (81.4% female, mean age 58.1)	167 (45% female, mean age 10.4)	104 (100% female, mean age 59.9)
Dosage and type of vitamin D	60,000 IU per week, orally	800 IU daily, oral D3	2000 IU daily, oral D 3	1200 IU daily, oral D3	2000 IU daily
ITR / influenza assessment method	Clinical diagnosis	Self-report in the questionnaire 18 (median) months after randomization	Self-report in the biweekly questionnaire	Nasopharyngeal swab by the doctor	Self-report during visit to the doctor every 6 months
Significant reduction in ITR or influenza	Y	N	N	Y	Y
P-value	<0,005 *	0,06	0,56	0,04 *	<0,002 *
95% CI	N / D	0,64–1,01	-2,4 a 3,4	0,34-0,99	N / D

NRCT = Non-randomized controlled trial, RCT = Randomized controlled trial.

* P-values less than 0.05 considered significant.

Source: BEARD, BEARDEN, STRIKER, (2012)

Studies by Beard, Bearden, Striker (2012), and summarized in Table 1, concluded that there is a direct relationship between the single nucleotide polymorphisms of the vitamin D receptor (VDR) and the worsening of infections. This finding concludes that this is related to the action vit D3 modulator of the innate response. Other studies argue that the high mortality rate due to COVID-19 infection suggests a relationship with serum vitamin D level and the immunoregulatory effect of vit D helps to control and reduce the worsening of the coronavirus [44].

A 30 ng / ml dose of vitamin D is more recommended for people in risk groups, composed mainly of pregnant women, the elderly, patients with osteoporosis, inflammatory and autoimmune diseases, chronic and pre-atrial kidneys. The dose should be prescribed by a doctor in order to avoid problems related to excess, such as hypervitaminosis, which can cause the appearance of kidney stones, weakening of the bones and metabolic disorders. Treatment should also include eating healthy foods including fish and eggs, in addition to seeking sun, which is the natural activator of vitamin D and which will contribute to the absorption of calcium [9, 10, 11, 13].

4.1 CORONAVIRUS AND VITAMIN D AS A FIGHTING FACTOR

Wuhan is a port city in the interior of China and is home to the best universities of science and technology. It has a powerful market for the sale of live animals and seafood, mainly wild animals, such as the pangolin. It is believed that this animal was responsible for the initial contamination in humans. Such animals are sold as food and as an integral part of oriental medicine however, it is traded illegally. This animal presented a viral strain with a 99% genetic similarity to the new coronavirus. It is impossible to say with conviction that the virus passed from an animal to a human in the Wuhan market because it is not known which the animal it was not who patient zero was, that is, the first person infected [7, 8, 19, 45, 46 47].

Coronavirus has a high rate of contagion and one person has the power to infect five other healthy people, with each infected person shaping this virus spread factor. If transmission occurs at the same time, contamination occurs exponentially and this can contribute to the collapse of health systems. This is one of the reasons for the application of social isolation, as one of the tools used to control the rate of transmission of the coronavirus and thus avoid chaos in public health services. This is having relative success in some countries, with adherence by the majority of the population [9, 11, 19, 47].

Human-to-human transmission occurs mainly among family members, with the inclusion of relatives, friends

and other people who somehow come into close contact with sick and / or infected people and who are in the incubation period of the virus [9, 10, 11].

After China enforced social isolation, starting with the locking up of the city of Wuhan on January 23, there was a reduction in the number of cases of contamination, and from March 8, 2020 this fell to dozens. This demonstrates that the measure was correct and had positive effects, stabilizing the number of cases and subsequently the return to normal activities. Cases of transmission grew once again due to the return to China of people from epidemic regions [9, 11, 46].

In a study carried out among people with SARS, it was observed that 17% of the patients required mechanical ventilation and 5% died. The health system of a nation / state / city does not have hospital beds for the entire population because people in general are healthy. Only a minority have or develop diseases requiring hospital beds. For some people who come into contact with viruses, their body creates antibodies with the ability to fight the virus. They become asymptomatic for the diseases generated by these organisms, but they still have the ability to transmit the virus to people who come into direct contact with them and this requires awareness and some care in order to hinder transmission [9, 11, 48].

People who work and/or deal directly with sick people with COVID-19 run a high risk of becoming infected due to their close contact and due to the high rate of transmission of the virus. In China, by February 14, 2020, more than 1,716 healthcare workers had been infected, with 1,502 from Hubei province and 1,102 from Wuhan, with a total of six deaths. Another group of people with potential for infection are those who work in the health system; doctors, nurses, security, cleaning and food service personnel, among others. They can spread this virus to several places as they travel from their communities to work and back home. This tends to generate an outbreak only among the components of this group [9, 10, 11, 47].

Health care workers tend to have low concentrations of 25 (OH) D, as a result of working long periods indoors. This was seen among nurses at a children's hospital in Iran, who had an average concentration of 12 +/- 9 ng / ml. However, in the United States of America doctors had a concentration of 22 +/- 2 ng / ml, while nurses and other health professionals had 25 +/- 4 ng / ml. Transmission among health professionals, in most cases, is due to hospital infection. In China, only 3.8% of cases were transmitted by patients with COVID-19 [9, 10, 11].

Recent magazine articles mention that infection by COVID-19 produces an increase in the production of

proinflammatory cytokines, C-reactive protein, an increased risk of pneumonia, sepsis, respiratory distress syndrome, diabetes and hypertension, with these symptoms associating almost simultaneously [9, 11, 47].

According to Grant et al. (p.8, 2020), the main epidemiological characteristics of the COVID-19 outbreak in China until February 2020 were as follows:

- The lethality rate (CFR) increased by 0.2% for young patients under the age of 40 and 14.8% for the elderly aged 80 and over
- The CFR was higher for men than for women (2.8% x 1.7%)
- Having comorbidities contributed to a significant increase in CFR (N = none, 0.9%; cancer, 5.6%; hypertension 6.0%; chronic respiratory tract infection (chronic RTI), 6.3%; diabetes melitus, 7.3%, cardiovascular disease [CVD], 10.5%).

The monotonic increase in CFR may be related to the presence of chronic diseases, which tends to appear and increase its effects due to the increase in the age or aging of people, who tend to reduce the serum concentration of 25 (OH) D. Other factors may also be associated with changes related to age in relation to the innate immune response, where the response increases the production of cytokines with the aging of people. Young children are more susceptible to influenza A as a result of the difference in the innate immune response [9, 11, 49].

People who have chronic illnesses usually have a low concentration of 25 (OH) D and increased inflammation. In the city of Trieste, Italy, a study was carried out with the elderly with a mean age of 67 +/- 12 years of age, who developed acute myocardial infarction and presented mean serum concentrations of 25 (OH) D of 11 + in winter / - 2 ng / ml. In the study conducted in Wenzhou, China, with the group of people with diabetes, the age was 43 +/- 11 years old and with the mean serum concentrations of 25 (OH) D, the value found was 13 ng / ml, and 16 ng / ml for control subjects [9, 11, 50].

When the COVID-19 injures the lung epithelial cells, it facilitates the occurrence of pneumonia, by increasing the production of Th1 type cytokines, which responds innately to viral infections with an increase in cytokines. In cell studies carried out in the laboratory, it was observed that at the late stage of the SARS-CoV pathology, and that responsible for the lung injury was interferon [9, 10, 11, 31].

Few, if any foods, are enriched with Vitamin D and few people take vitamin D supplements. The ban on fortifying foods with vitamin D occurred after the Second World

War, due to the intoxication of children and adolescents as a result of their excessive dose in milk. Vitamin D reduces the risk of death in RTI-related pandemics according to results found in the 1918-1919 influenza pandemic studies in the United States of America [9, 11, 14].

Some evidence points to the fact that Vitamin D supplementation and higher concentrations of 25 (OH) D may be linked to a reduced risk of several chronic diseases such as cancer, diabetes mellitus, among others. A higher level of vitamin D is inversely associated with infection caused by viruses such as dengue, hepatitis, HIV, influenza, rotavirus, among others [9, 11, 43].

In order to increase serum concentrations of 25 (OH) D, which has the ability to help reduce infections acquired due to COVID-19, vitamin D supplementation is recommended. In studies, the recommended concentrations are at least 40- 50 ng / ml (100-125 nmol / l). This enables the prevention of infections and thus lowers the likelihood of their spread, serving people who work directly in the fight against coronavirus, including those who deal with sick people in homes and people who are quarantined and / or infected [9, 10, 11].

The main mechanisms for reducing the risk of infections and microbial death provided by vitamin D are: physical barrier, natural cellular immunity and adaptive immunity. It also helps to maintain tight joints, gaps and sticking joints. Viruses tend to disturb the integrity of the joints, with the power to increase infection by the virus and other microorganisms, whose viral action progress to pneumonia [9, 11, 51].

Vitamin D plays an important role in natural cellular immunity due to the induction of antimicrobial peptides, a group which includes human cathelicidin, LL-37 via 1,25-dihydroxyvitamin D and defensins. The function of host-derived peptides is to kill invading pathogens, acting by disturbing the invader's cell membranes and which can neutralize the biological activities of the endotoxin [9, 11, 52].

Serum concentrations of 25 (OH) D fall with the increasing age of people or aging of the individual due to the lack of exposure to the sun, in addition to the natural reduction of vitamin D production. This is due to the lower levels of 7-dehydrocholesterol in the skin. Also certain drugs can lead to a reduction in serum concentrations of 25 (OH) D, such as antibiotic drugs, anti-inflammatory agents, antiepileptics, antiretroviral drugs, anti-hypertensive drugs, endocrine drugs and some herbal medicines, among others, which are consumed as people get older [9, 11, 53].

Vitamin D supplementation also has the power to improve the expression of genes that are related to antioxidation. It

influences the increase in glutathione production and avoiding the use of ascorbic acid, which has among its functions antimicrobial activity [9, 11, 48].

V. CONCLUSION

One of the ways to protect the body against COVID-19 and other viruses and to reduce the vulnerability of the body as well as to strengthen the immune system against diseases, is to adjust the intake of vitamins and minerals, mainly C, D and Zinc that work as system optimizers.

In winter there is a peak of viral illnesses such as influenza that attack the respiratory tract system. Climatic conditions of low temperature and relative humidity are conditions that allow the virus to survive for a longer time outside the body, when compared to hotter seasons. During this period, a person has less access to the sun's rays, reducing the concentrations of 25 (OH) D, which can increase the risk of developing the flu. The most vulnerable population group for COVID-19 is the one with the greatest vitamin D deficiency. This group is composed of the elderly and people with existing comorbidities, such as diabetes mellitus, chronic respiratory disease, cardiovascular disease and cancer, among others.

Vitamin D plays an important role in maintaining human immunity, which helps the body to defend itself against other viruses and specifically against COVID-19. This makes it an ally in the fight against SARS-CoV-2, mainly for the elderly, with the ability to neutralize the damage caused by diseases resulting from complications in the respiratory tract system. It plays an important role in protecting against respiratory infections and vitamin D supplementation can serve as protection against COVID-19 infection.

In the current quarantine, with the recommendation by the authorities to stay at home, people should seek to consume healthy foods that have some vitamin D content such as fish and eggs, as well as take time to sit in the sun by windows and doors of the homes. To avoid skin problems, sunscreen should be used.

Coronavirus has a high rate of contagion in relation to influenza, MERS-CoV and SARS. This can lead to health system collapse if the virus is transmitted to the population all at the same time. One of the ways to avoid contagion is through non-pharmaceutical solutions, such as covering the mouth and nose when coughing and sneezing with something other than a hand, avoiding close contact and placing yourself at a minimum distance of 1.5 m from someone else, frequent handwashing with soap and water

or using 70%, alcohol gel, cleaning surfaces touched frequently and finally using a face mask.

The older population is more prone to morbidity and mortality and should be the group that require greater care. In groups with healthy and robust immune systems, the effect of the virus tends to be asymptomatic, but just like other groups there is a high risk of contagion.

Direct contact with virus carrying host animals or wild animal consumption is assumed to be the primary transmitter of SARS-CoV-2. Human contact with sick patients or infected people, or during the incubation period of the virus are the main mechanisms of transmission of the coronavirus. There are dozens of vaccines under study around the world, but the scientific community are developing the most appropriate and effective one to fight the virus.

The world is working to discover medicines and vaccines to fight coronavirus, a disease that has already spread to more than 205 countries around the world on almost every continent, with the exception of Antarctica.

However, further studies are still needed to determine the risks and necessary vitamin D replacement benefits, progress needs to be made in studies about vitamin D to validate its efficiency, in the literature there are few studies, in the long run, greater understanding is needed.

REFERENCES

- [1] Barral, D, Barros, A. .C & Araujo, R. .P. .C. (2007 Sep./Dec.). Vitamin D: a molecular approach. *Pesq Bras Odontoped Clín Integr*, 7(3), 309-315. Retrieved 3 Apr, 2020, from <https://bit.ly/2T4mZMM>.
- [2] Marques et al.. (2010). The importance of vitamin D levels in autoimmune diseases. *Rev Bras Reumatol*, 50(1), 67-80. Retrieved 3 Apr, 2020, from <https://bit.ly/2Tmh3z1>.
- [3] Castro, L. .C. .G. (2011 Nov.). The vitamin D endocrinological system. *Arq Bras Endocrinol Metab*, 55(8), 566-575. Retrieved 3 Apr, 2020, from <https://bit.ly/2y23SvB>.
- [4] Lichtenstein et al.. (2013). Vitamin D: non-skeletal actions and rational use. *Rev Assoc Med Bras*, 59(5), 495-506. Retrieved 3 Apr, 2020, from <https://bit.ly/2yTGkt2>.
- [5] Maeda et al.. (2014 Jul.). Recommendations of the Brazilian Society of Endocrinology and Metabology (SBEM) for the diagnosis and treatment of hypovitaminosis D. *Arq Bras Endocrinol Metabol*, 58(5), 411-433. Retrieved 27 Apr, 2020, from <https://bit.ly/2KTy5zw>.
- [6] Reis, C. F. A. & Guimarães, F. P. (2017). Multiple sclerosis patient's perception about the use of vitamin d in clinical therapy. *Medicine*, 5 (1). Retrieved 27 Apr, 2020, from <https://bit.ly/2Z0nyLc>.

- [7] World Health Organization. (2020). Coronavirus disease (COVID-19) outbreak. Retrieved 27 Apr, 2020, from <https://bit.ly/2xU8u6U>.
- [8] Centers for Disease Control and Prevention (2020). Coronavirus disease 2019 (COVID-2019). Retrieved 14 Apr, 2020, from: <https://bit.ly/3ch0R9vl>.
- [9] Grant et al.. (2020 Mar. 15). Vitamin D supplementation prevent and treat influenza, coronavirus, and pneumonia infections. Preprints, 19(1), 1-32. Retrieved 16 Apr, 2020, from <https://bit.ly/2WwKUQo>.
- [10] Guo et al.. (2020 Mar 13). The origin, transmission and clinics therapies on coronavirus said 2019 (COVID-19) outbreak - an update on the status. *Mil Med Res*, 7(1), 1-10. Retrieved 16 Apr, 2020, from <https://bit.ly/2Z2RoPq>.
- [11] Grant et al. (2020 Apr. 2). Evidence that vitamin D supplementation could reduce risk of influenza and COVID-19 infections and deaths. *Nutrients*, 12(4) 988. Retrieved 22 Apr. 2020, from DOI:10.3390/nu12040988.
- [12] Bryson, K. J., Nash, A. A & Norval, M. (2014). Review Article: Does vitamin D protect against respiratory viral infections?. *Epidemiology and Infection*, 142(9), 1789-1801. Retrieved 22 Apr. 2020, from <https://bit.ly/2X04Pgn>.
- [13] Nair M. & Maseeh A. (2012 Apr./Jun.). Vitamin D: The "sunshine" vitamin. *J Pharmacol Pharmacother*. 3(2) 118-126. Retrieved 22 Apr. 2020, from <https://bit.ly/3giYC7Z>.
- [14] Unger, M. D. (2009). Determination of serum vitamin D levels in a sample of healthy individuals from the Brazilian population. PhD thesis - Faculty of Medicine. University of Sao Paulo. São Paulo, SP, Brazil. Retrieved 22 Apr. 2020, from <https://bit.ly/2VVUUHY>.
- [15] European Centre for Disease (2020). Prevention and Control. Factsheet for health professionals on coronaviruses - ECDC - European Union. Retrieved 12 Apr. 2020, from <https://bit.ly/3axsHO1>.
- [16] Desforges et al. (2020 Jan.). Human coronaviruses and other respiratory viruses: underestimated opportunistic pathogens of the central nervous system? *Viruses*, 12 (1). Retrieved 12 Apr. 2020, from <https://bit.ly/2X3E6Qb>.
- [17] Monto, A. S., Cowling, B. J. & Peiris, J. S. M. (2014 Feb. 27). Coronaviruses. *Viral Infections of Humans*. 199-223. Retrieved 27 Apr. 2020, from <https://bit.ly/2TxSmQb>.
- [18] Li, H. et al., (2020). Coronavirus disease 2019 (COVID-19): current status and future perspectives. *Int J Antimicrob Agents*. 55(5) 105951. Retrieved 24 May. 2020, from <https://bit.ly/2A9xOGw>.
- [19] Zheng J. (2020). SARS-CoV-2: an Emerging Coronavirus that Causes a Global Threat. *Int J Biol Sci*. 16(10) 1678-1685. Retrieved 29 Apr. 2020, from <https://bit.ly/2AP9jPl>.
- [20] Gil, A C. (2010). How to design research projects. 5. ed. São Paulo: Atlas.
- [21] Mourão et al.. (2005). Bioavailability of fat-soluble vitamins. *Rev Nutr [Online]*, 18(4), 529-539. Retrieved 3 Apr, 2020, from <https://bit.ly/3brFXmQ>.
- [22] Cabral, M. A. et al., (2013 Oct. 3). Prevalence of vitamin D deficiency during the summer and its relationship with sun exposure and skin phototype in elderly men living in the tropics. *Clin Interv Aging*. 8 1347–1351. Retrieved 30 Apr. 2020, from <https://bit.ly/2yyEPAY>.
- [23] Andriolli, T. V. (2018). Serum concentrations of 25 hydroxyvitamin D in women over 35 years old: prevalence of values considered normal and associated factors. 2018. 146 f. Dissertation of Master - Faculty of Public Health. University of Sao Paulo. São Paulo, SP, Brazil. Retrieved 22 abr. 2020, <https://bit.ly/3aq50WY>.
- [24] Maravilhas, I. A. P. (2017). Vitamin D: polymorphisms in the VDR gene and pathological consequences. Thesis of Master - Instituto Superior de Ciências da Saúde Egas Moniz. Soules. Almada, Portugal. Retrieved 24 Apr. 2020, from <https://bit.ly/3dJbpzA>.
- [25] Evans et al.. (2018 Mar). Vitamin D3 supplementation reduces subsequent brain injury and inflammation associated with ischemic stroke. *Neuromolecular Med*, 20(1), 147-159. Retrieved 10 Apr. 2020, from <https://bit.ly/3cxomep>.
- [26] Stagi, S & Rigante, D. (2018 Mar). Vitamin D and juvenile systemic lupus erythematosus: lights, shadows and still unresolved issues. *Autoimmun Rev*, 17(3), 290-300. Retrieved 12 Apr. 2020, from <https://bit.ly/2WwX7uZ>.
- [27] Goltzman, D. (2018 Apr). Functions of vitamin D in bone. *Histochem Cell Biol*, 149(4), 305-312. Retrieved 18 Apr. 2020, from <https://bit.ly/3bzY2iy>.
- [28] Bikle, M. D. (2017 Agu. 11). Vitamin D: production, metabolism, and mechanisms of action. *Endotext [Internet]*. Retrieved 30 Apr. 2020, from <https://bit.ly/2ZyHqFy>.
- [29] Bertolini, D. J. L. & Tzanno-Martins, C. (2000 Sep). Revision: immunomodulator effect of vitamin D. *J bras nefrol*, 22(3), 157-161. Retrieved 9 Apr. 2020, from <https://bit.ly/2xRINnr>.
- [30] Barragan, M., Good, M., & Kolls, J. K. (2015 Sep.). Regulation of dendritic cell function by vitamin D. *Nutrients*. 7(9) 8127–8151. Retrieved 30 Apr. 2020, from <https://bit.ly/2ZzmYVv>.
- [31] Russel, B. et al. (2020). Associations between immune-suppressive and stimulating drugs and novel COVID-19—a systematic review of current evidence *ecancer* 14 1022. Retrieved 24 May. 2020, from <https://bit.ly/3d5YLtG>.
- [32] Dantas, A. T., Duarte, A. L. B. P., & Marques, C. D. L. (2009). Vitamin D in rheumatoid arthritis and systemic lupus erythematosus. *Temas Reumatol Clin*, São Paulo, 10(2), 53-59.
- [33] Bellan, M, Pirisi, M & Sainaghi, P. J. (2015). Osteoporosis in rheumatoid arthritis: role of the vitamin D/parathyroid hormone system. *Rev Bras Reumatol*, 55(3), 256–263. Retrieved 22 Apr. 2020, from <https://bit.ly/3fLAn2d>.
- [34] Bae, S. C. & Lee, Y. H. (2018 Jan.). Association between Vitamin D level and / or deficiency, and systemic lupus erythematosus: a meta-analysis. *Cell Mol Biol (Noisy-le-grand)*, 64 (1) 7-13. Retrieved 2 Apr. 2020, from doi: 10.14715 / cmb / 2018.64.1.2.

- [35] Sassi, F., Tamone, C. & D'Amelio. (2018 Nov.). Vitamin D: nutrient, hormone, and immunomodulator. *Nutrients*. 10(11) 1656. Retrieved 30 Apr. 2020, from <https://bit.ly/3cZAdSX>.
- [36] Terrier et al. (2012 Oct). Restoration of regulatory and effector T cell balance and B cell homeostasis in systemic lupus erythematosus patients through vitamin D supplementation. *Arthritis Res Ther*, 14 (5) R221. Retrieved 1 Apr. 2020, from doi: 10.1186 / ar4060.
- [37] Mak A. (2018 Aug.). The impact of vitamin D on the immunopathophysiology, disease activity, and extra-musculoskeletal manifestations of systemic lupus erythematosus. *Int J Mol Sci*. 19(8) 2355. Retrieved 30 Apr. 2020, from <https://bit.ly/2ZyUY48>.
- [38] Gorbalenya, A. E. et al. (2020 Mar. 2). The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. *Nat Microbiol*. 5 536-544. Retrieved 29 Apr. 2020, from <https://go.nature.com/2Tz4EHX>.
- [39] Hossain, M & Min, R. .M. (2000 Mar). Coronavirus: symptoms, diagnosis, treatment and prevention. *Journal of Medical Internet Research*. Retrieved 16 Apr. 2020, from <https://doi.org/10.2196/preprints.18924>.
- [40] Lippi, G. & Plebani, M. (2020). Laboratory abnormalities in patients with COVID-2019 infection. *Clinical Chemistry and Laboratory Medicine (CCLM)*, 20200198. Retrieved: 15 Apr. 2020, from doi: <https://doi.org/10.1515/cclm-2020-0198>.
- [41] Martins-Filho, P.R., Tavares, C. S. S., & Santos, V. S. (2020 Apr. 23). Factors associated with mortality in patients with COVID-19. A quantitative evidence synthesis of clinical and laboratory data. *Eur J Intern Med*. Retrieved 24 May. 2020, from <https://bit.ly/3ejv2xd>.
- [42] Beard, J. .A, Bearden, A & Striker, R. (2011 Mar). Vitamin D and the anti-viral state. *J Clin Virol*, 50(3), 194-200. Retrieved 8 Apr. 2020, from <http://dx.doi.org/10.1016/j.jcv.2010.12.006>.
- [43] Wimalawansa, S. J. (2016 Jun. 23). Vitamin D Adequacy and improvements of comorbidities in persons with intellectual developmental disabilities. *J Child Dev Disord*. 2: 3. Retrieved 24 May. 2020, from <https://bit.ly/2A0s0iJ>.
- [44] Braiman, M. (2020). Latitude dependence of the COVID-19 mortality rate — A possible relationship to vitamin D deficiency?. SSRN. Available at: <http://dx.doi.org/10.2139/ssrn.3561958>. Retrieved 3 Apr. 2020, <http://dx.doi.org/10.2139/ssrn.3561958>.
- [45] Lopes, R. J. (2020 Mar.). Pangolin may be missing link between coronavirus and humans, says new research. *Newspaper. São Paulo*. Retrieved 29 Mar. 2020, from <https://bit.ly/2UyJdYc>.
- [46] McCarthy et al. (2020 Feb.). Coronavirus: how disease X, the epidemic-in-waiting, erupted in China. *South China Morning Post*. Retrieved 27 Apr. 2020, from <https://bit.ly/3bYIV4F>.
- [47] Tufan, A., Güler, A. A. & Matucci-Cerinic. (2020). COVID-19, immune system response, hyperinflammation and repurposing antirheumatic drugs. *Turk J Med Sci*. 50(3): 620–632. Retrieved 24 May. 2020, from <https://bit.ly/2TB0xuR>.
- [48] Tan, B. L. et al. (2018). Antioxidant and Oxidative Stress: A Mutual Interplay in Age-Related Diseases. *Front Pharmacol*. 9: 1162. Retrieved 24 May. 2020, from <https://bit.ly/36ta6Bo>.
- [49] Wang, H. et al., (2017 May). Vitamin D and Chronic Diseases. *Aging Dis*. 8(3): 346–353. Retrieved 24 May. 2020, from <https://bit.ly/3eeQMKJ>.
- [50] Aksan, A. et al., (2020 Feb.). Measuring Vitamin D Status in Chronic Inflammatory Disorders: How does Chronic Inflammation Affect the Reliability of Vitamin D Metabolites in Patients with IBD? *J Clin Med*. 9(2): 547. Retrieved 24 May. 2020, from <https://bit.ly/2zr6yDE>.
- [51] Wu, D. et al. (2018). Nutritional Modulation of Immune Function: Analysis of Evidence, Mechanisms, and Clinical Relevance. *Front Immunol*. 9:3160. Retrieved 24 May. 2020, from <https://bit.ly/2Xuna5z>.
- [52] Chung, C. (2020 Apr.). Vitamin D-Cathelicidin Axis: at the Crossroads between Protective Immunity and Pathological Inflammation during Infection. *Immune Netw*. 20(2):e12. Retrieved 24 May. 2020, from <https://bit.ly/2LRVr9v>.
- [53] Mendes, M. M. et al. (2018). Vitamin D status in the Tropics: Is sunlight exposure the main determinant? *Nutrition Bulletin*. 43: 428-434. Retrieved 24 May. 2020, from <https://bit.ly/3ghKOKY>.